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ARTICLE

Pharmacogenetics of Schizophrenia

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Patients display significant differences in response to therapeutic agents which may be caused by a variety of factors. Among them, genetic components presumably play a major role. Pharmacogenetics is the field of research that attempts to unravel the relationship between genetic variation affecting drug metabolism (pharmacokinetic level) or drug targets (pharmacodynamic level) and interindividual differences in pharmacoresponse. In schizophrenia, pharmacokinetic studies have shown the role of genetic variants of the cytochrome P450 enzymes CYP2D6, CYP2C19, and CYP2C9 in the metabolism of neuroleptic drugs. At the level of the drug target, variants of the dopamine D3 and D4, and 5-HT2A and 5-HT2C receptors have been examined. A general problem of pharmacogenetic studies in schizophrenia is the high number of controversial findings which may be related to the lack of standardized phenotype definition. Recently, guidelines for an exact and comparable phenotype characterization have been proposed and will aid in designing and evaluating pharmacogenetic studies in the future. The final goal of pharmacogenetic studies—making a prediction of drug response at the level of the individual patient—will require a simultaneous look at a large number of response-determining genetic variants by applying the tools of pharmacogenomics, e.g. large-scale Single Nucleotide Polymorphism (SNP) detection and genotyping. Am. J. Med. Genet. (Semin. Med. Genet.) 97:98–106, 2000.

KEY WORDS: pharmacogenomics; cytochrome P450 enzymes; dopamine receptors; serotonin receptors; SNP

INTRODUCTION

As a result of exposure to many therapeutic agents, patients display significant differences in response and suffer adverse effects. The observed patient-to-patient differences may be caused by a variety of factors. Among them, genetic components presumably play a major role. That is the underlying hypothesis of pharmacogenetics that attempts to unravel the relationship between genetic variation affecting drug metabolism (pharmacokinetic level) or drug targets (pharmacodynamic level) and differences in pharmacoresponse. The relationship between adverse drug reactions and genetically determined variation was first demonstrated in the 1950s [Motulsky, 1957], when the introduction of new technologies enabled the identification of variation in drug-metabolizing enzymes and discrimination of diverse drug metabolites. In 1959, Vogel coined the term "pharmacogenetics" for this new field of research [Vogel, 1959].

In the subsequent decades, more variations of drug-metabolizing enzymes than of drug targets were reported. The relative absence of data regarding variation of target proteins can lead to the conclusion that pharmacokinetic rather than pharmacodynamic variation is primarily responsible for interindividual differences in drug response. The paucity of pharmacogenetic phenomena on the pharmacodynamic level, however, may be explained by the fact that the chemistry allowing the study of drug metabolism is much older than the means to investigate receptors and other target proteins [Propping and Kopun, 1973; Kalow, 1997; Levy, 1998]. Only more recently has the rapid progress of the Human Genome Project as well as the technical progress in methods of DNA analysis provided the tools for identifying genetic variation at the level of the drug target and has opened up a new perspective for pharmacogenetics [Propping and Nöthen, 1995].

Recent progress has provided the tools for identifying genetic variation at the level of the drug target.

With respect to psychiatric disorders such as schizophrenia, the genetic variation of drug targets expressed in the central nervous system (approximately 30,000 proteins) is of particular interest. Recent systematic studies of genetic variation [Nickerson et al., 1998; Cargill et al., 1999; Halushka et al., 1999] provide a rough estimate about the frequency of mutational alterations in the genome. Based upon

Dedicated to Friedrich Vogel at the occasion of his 75th birthday. Friedrich Vogel coined the term "pharmacogenetics" in 1959.

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these studies, the frequency of single nucleotide polymorphisms (SNPs) in coding regions can be estimated to be 1 in 1,000–2,000 bp (bearing in mind that the variability between genes may differ substantially). Of these variants, about 40–50% lead to replacement of an amino acid residue and potentially impact protein function. Given the extent of genetic variation in combination with the huge number of potential drug targets in the brain it may be hypothesized that the magnitude of target variation substantially exceeds metabolic mechanisms.

Pharmacogenetics has become recognized as a significant concept for the development of new and individually tailored drugs.

Very recently, the field of pharmacogenetics has entered into a new era when it became recognized as a significant concept for the development of new and individually tailored drugs. Applying the large-scale systematic approaches of genomics to the basic concept of pharmacogenetics, the discipline of pharmacogenomics was created [Housman and Ledley, 1998; Persidis, 1998; Kleyn and Vesell, 1998; Evans and Relling, 1999]. The essential difference between pharmacogenetics and pharmacogenomics is that pharmacogenetics has approached the problem from the phenotypic level, whereas pharmacogenomics focuses on the DNA level.

In schizophrenia, many researchers have been engaged in identifying genetic factors that may influence response and adverse effects for well established neuroleptic drugs. The present article aims at discussing pharmacogenetic studies that have traditionally been performed at the pharmacokinetic and only recently at the pharmacodynamic level.

POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES

It has been known for a long time that there is large interindividual variation in elimination rates, steady state concentrations and biotransformation of pharmaceuticals. This applies particularly to the lipophilic drugs acting on the central nervous system that are extensively metabolized by cytochrome P450 (CYP) enzymes. The variation can, in many cases, be accounted for by null or variant alleles resulting from mutations in genes and coding these enzymes.

Most drug-metabolizing enzymes exhibit clinically relevant genetic polymorphisms. Essentially, one has to differentiate between enzymes responsible for modification of functional groups (phase I reactions) and those responsible for conjugation with endogenous substituents (phase II reactions). Cytochrome P450 enzymes, aldehyde and alcohol dehydrogenases, and esterases belong to the former group, whereas *N*-acetyltransferase, glutathione s-transferase, and catechol *O*-methyltransferase belong to the latter group [Evans and Relling, 1999]. Although only a limited number of pharmacogenetic traits could be delineated in the past, advanced methods from molecular genetics, biochemistry, and clinical pharmacology have the power to pin down so far uncovered genetic variation of drug metabolism in the future.

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Polymorphisms related to metabolism of drugs used in psychiatry are known for CYP2C9 (wild-type enzyme and two variants), CYP2C19 (two variants), and CYP2D6 (many variants), also known as the debrisoquine/sparteine polymorphism [Coutts and Urichuk, 1999; Yasar et al., 1999; Yasumori et al., 1999]. For each of these enzymes, extensive and poor metabolizers (EM, PM) exist, with PM-alleles behaving in a recessive, EM-alleles in a dominant way. Thus, individuals with a PM phenotype are either homozygous or compound heterozygous for PM alleles; individuals with an EM phenotype are either homozygous for the wild-type allele or heterozygous wild-type/PM.

Neuroleptics as Substrates of CYP2D6

From the clinical point of view the polymorphism of CYP2D6 is by far the best characterized. Five to ten percent of Europeans, about 2% of Asians, and 7–8% of Africans are poor metabolizers of debrisoquine/sparteine, because they produce a functionally abnormal, an inactive enzyme, or completely lack the enzyme [Llerena et al., 1996; Marez et al., 1997]. It is an important question to what extent the CYP2D6 polymorphism influences neuroleptic therapy. Phenotyped panel studies have shown that the disposition of the neuroleptics haloperidol, perphenazine, zuclopenthixol, thioridazine, and risperidone cosegregates with that of debrisoquine [Fang and Gorrod, 1999]. In healthy subjects the kinetic profiles of these compounds after single doses markedly differ between EM and PM phenotypes, thus explaining, in part, the variation in their clearance. PMs of debrisoquine achieve higher plasma concentrations and more side effects of the neuroleptics perphenazine and thioridazine than EMs [Dahl and Bertilsson, 1993]. Among psychotic patients who had experienced unwanted effects such as excess sedation, postural hypotension, and autonomic effects within the first few days of treatment with antipsychotics an overrepresentation of PMs was found [Spina et al., 1992a,b]. On the other hand, it is not clear whether the development of tardive dyskinesia after long-term neuroleptic administration is associated with a reduced metabolizing capacity of CYP2D6 [Arthur et al., 1995; Andreassen et al., 1997; Armstrong et al., 1997; Kapitany et al., 1998; Ohmori et al., 1998].

All present-day neuroleptics undergo extensive oxidative metabolism in the liver, and many of them have pharmacologically active metabolites. Chlorpromazine is probably the most extensively studied phenothiazine antipsychotic drug, with some 45 metabolites identified in human studies [Fang and Gorrod, 1999]. Haloperidol is one of the most commonly used drugs in psychiatry world-wide. It is metabolized by reduction to form reduced haloperidol that is also pharmacologically active. Although the metabolism by CYP2D6 is only a minor pathway for haloperidol [Pan and Belpaire, 1999] the plasma half life of both haloperidol and reduced haloperidol was found to be longer in PMs than in EMs [Llerena et al., 1996].

Similar to the classic neuroleptics, the atypical antipsychotic clozapine exhibits large interindividual variations in bioavailability, steady-state plasma concentrations, and clearance. Besides other factors such as gender, age, and smoking, genetic factors might contribute to the observed variation. Clozapine is metabolized by several CYP enzymes, including the polymorphic CYP2D6 and CYP2C19 [Fang and Gorrod, 1999; Prior et al., 1999]. The metabolic pathway, however, is not entirely clear. There is a general paucity of in vivo data regarding the metabolism of the other new atypical antipsychotics, including risperidone, olanzapine, quetiapine, and sertindole, indicating a need for further research in this area [Prior et al., 1999]. In any case, the combined application of drugs metabolized by CYP2D6 such as neuroleptics or antidepressants may lead to potentially dangerous pharmacokinetic interactions, particularly when the patient is a poor metabolizer. Historically, the CYP2D6 PM or EM genotypes were inferred through debrisoquine/sparteine loading. Some antipsychotic agents are competitive inhibitors of CYP2D6-mediated oxidation of these probe drugs. Individuals of the EM phenotype may even be transformed to apparent PMs [Alfaro et al., 1999]. Thus, "genotyping" with probe drugs may not be as reliable as molecular genetic testing.

Role of CYP2D6 in the Brain

For many genetic polymorphisms of drug-metabolizing enzymes there is no evident phenotype in the absence of a drug challenge, perhaps because these enzymes are not critical for metabolism of endogenous compounds. It was hypothesized, however, that due to their inherited defect poor metabolizers have a weakness in synthesizing endogenous morphine via CYP2D6 because CYP2D6 is also expressed in the brain [Sindrup et al., 1993]. To date, however, no association could be found to psychiatric disease.

Inter-Ethnic Differences

The variation in the frequency of PM alleles in the different ethnic groups is clearly responsible for the varying frequencies of the PM phenotype. The high frequency of a certain CYP2D variant in Chinese results in a slower average hydroxylation of debrisoquine and of haloperidol in the EM group [Johansson et al., 1994; Mihara et al., 1999]. When prescribing haloperidol or other neuroleptics metabolized by CYP2D6 to individuals of Asian ancestry, physicians should take into account that Asians on the average develop higher plasma levels than Europeans and thus have an increased sensitivity to these agents [Potkin et al., 1984; Frackiewicz et al., 1997].

DRUG TARGETS

In principle, all receptor genes or subunit genes for neurotransmitters such as dopamine, serotonin, glutamate, GABA, catecholamines etc. as well as the genes that are located downstream in the intracellular signaling pathways can be considered candidate genes for pharmacogenetic studies in schizophrenia. To investigate the potential involvement of a specific candidate gene in drug response or occurrence of side effects, it is required that genetic variation has been identified for this gene. Among the large number of potential candidate genes, the dopamine and serotonin (5-HT) receptors have been most extensively studied for the presence of genetic variation. This resulted in the identification of several genetic variants with potential functional significance (Tables I and II). Indeed, for many of these variants, it was shown by in vitro studies that the function of the receptor protein, as measured by ligand binding characteristics, intracellular cAMP production or calcium mobilization, is altered (Tables I and II). To date, variants of the dopamine D_3 and D_4, and 5-HT_{2A} and 5-HT_{2C} receptors have been examined in pharmacogenetic studies related to the treatment of schizophrenia.

Dopamine D_3 Receptor

Shaikh et al. [1996] reported an association between the Ser9/Ser9 genotype and failure to respond to clozapine. In a replication study, Malhotra et al. [1998] found a non-significant trend in the same direction. The authors speculated that insufficient power due to a small sample size may have prevented them from detecting a significant effect. Clearly, these findings suggest that further study of the dopamine D_3 receptor gene in clozapine response is warranted. The Ser9Gly polymorphism has also been implicated in the development of tardive dyskinesia suggesting a protective effect of the Ser9 allele [Steen et al., 1997; Basile et al., 1999; Segman et al., 1999]. This effect has not been found in a study from Germany [Rietschel et al., 2000].

Investigation of genes involved in drug response necessitates identification of genetic variants.

Dopamine D_4 Receptor

The 16 amino acid (aa) repeat of the D_4 protein does not seem to correlate with the degree of response to clozapine in patients resistant to typical neuroleptics [Shaikh et al., 1993; Rao et al., 1994; Rietschel et al., 1996]. A recent study

TABLE I.

Genetic Variants of Dopamine Receptors

Receptor	Variant	Frequency*	Functional consequence	Reference
D2	Val96Ala	<1%	Dopamine, chlorpromazine and clozapine binding ↓, inhibition of cAMP synthesis ↑	Gejman et al., 1994; Cravchik et al., 1999
	Pro310Ser	<1%	Inhibition of cAMP synthesis ↓	Gejman et al., 1994; Cravchik et al., 1996, 1999
	Ser311Cys	1–2%	Inhibition of cAMP synthesis ↓	Itokawa et al., 1993; Friedman et al., 1994; Gejman et al., 1994; Cravchik et al., 1996, 1999; Pohjalainen et al., 1997
	−141C Ins/Del	11%	Expression ↓	Arinami et al., 1997
D3	Ser9Gly	28%	Dopamine and GR99841 binding ↑	Lannfelt et al., 1992; Lundstrom and Turpin 1996
D4	Gly11Arg	1%	?	Cichon et al., 1995
	4 aa repeat	4% (1 repeat) 96% (2 repeats) <1% (3 repeats)	Influence on clozapine and quinpirole binding	Catalano et al., 1993; Hebebrand et al., 1997; Zenner et al., 1998
	7 aa deletion	<1%	?	Cichon et al., 1995
	13 bp deletion	2%	Loss of function	Nöthen et al., 1994a
	Val194Gly	12.5% (Africans)	Dopamine, clozapine and olanzapine binding ↓, insensitivity to guanine nucleotide suggests non-functional receptor	Seeman et al., 1994; Liu et al., 1996
	16 aa repeat	Highly polymorphic	Influence on sodium chloride sensitivity of clozapine binding and inhibition of cAMP synthesis	Van Tol et al., 1992; Lichter et al., 1993; Asghari et al., 1994, 1995
D5	Leu88Phe	<1%	Dopamine binding ↑, SCH-23390 binding ↓	Feng et al., 1998; Cravchik and Gejman 1999
	Ala269Val	<1%	No effect on agonist and antagonist binding	Sobell et al., 1995; Cravchik and Gejman 1999
	Pro330Gln	10% (Asians)	No effect on agonist and antagonist binding	Sobell et al., 1995; Cravchik and Gejman 1999
	Cys335Stop	<1%	Loss of function	Sobell et al., 1995
	Asn351Asp	<1%	Dopamine and risperidone binding ↓	Sobell et al., 1995; Cravchik and Gejman 1999
	Ser453Cys	<1%	No effect on agonist and antagonist binding	Sobell et al., 1995; Cravchik and Gejman 1999

*Frequencies apply to Caucasian populations if not otherwise stated.

by Cohen et al. [1999], however, reported differences in allele frequencies in patients showing a good response to typical agents versus those showing a good response to clozapine suggesting that D_4 might, in part, determine efficacy or side effects produced by different classes of antipsychotic drugs.

5-HT_{2A} Receptor

In the 5-HT_{2A} receptor, the three variants listed in Table II and a silent 102T/C change were tested for influence on the outcome of clozapine treatment. In support of a contribution of the 5-HT_{2A} receptor, Arranz et al. [1995, 1996] reported an overrepresentation of alleles 102C and 452Tyr among patients who did not respond satisfactorily to clozapine. The association between the silent 102T/C variant and clozapine response was not replicated by other groups [Masellis et al., 1995; Nöthen et al., 1995; Nimgaonkar

et al., 1996; Malhotra et al., 1996a], although in all studies the genotype and allele frequencies followed the same trend as the original finding. Meta-analysis of these studies showed a significant association between clozapine response and allele 102C [Arranz et al., 1998]. Recently published studies have not been able to resolve this issue because positive [Arranz et al., 1998; Joober et al., 1999] as well as negative data [Masellis et al., 1998; Lin et al., 1999] were reported. Because the 102T/C change does not cause an amino acid substitution in the receptor protein, it may reflect the effect on clozapine response of a functional variant elsewhere in the gene through linkage disequilibrium. A base change (G/A) at position −1438 of the 5-HT_{2A} promoter region has been detected that is in almost complete linkage disequilibrium with the 102T/C variant [Spurlock et al., 1998; own unpublished results]. The influence of this variant on the expression of the 5-HT_{2A} receptor is currently unclear because depending on the constructs used for the in vitro studies, different effects can be observed [Spurlock et al., 1998; own unpublished results]. Because the −1438G/A variant is in nearly full linkage disequilibrium with 102T/C the results with respect to clozapine response were similar [Arranz et al., 1997; Masellis et al., 1998]. The association of clozapine response with the His452Tyr variant was replicated in a Canadian study [Masellis et al., 1998], although two other studies found no significant differences [Nöthen et al., 1995; Malhotra et al., 1996a]. Meta-analysis of these studies supported a significant association between the 452Tyr allele and poor response to clozapine [Arranz et al., 1998].

Verification of positive findings in independent studies requires an exact and comparable phenotype characterization.

Interpretation of genotypic data from the 5-HT_{2A} receptor gene is complicated by the fact that the gene is subject to genomic imprinting and only the maternal gene copy is transcribed [Kato et al., 1996]. The picture is even more complex in the human brain where imprinting is seen in some individuals but not in others [Bunzel et al., 1998]. These findings have essential consequences for the evaluation of genetic studies in which the contribution of the 5-HT2A receptor gene to response to medications is analyzed, because the genotype may not in all cases reflect the actual expression pattern in brain.

After the field of pharmacogenetics is now about 40 years old, pharmacogenomics has entered the room.

5-HT_{2C} Receptor

Sodhi et al. [1995] reported a putative association of the 23Ser allele with response to clozapine, but later studies could not replicate this finding [Malhotra et al., 1996b; Rietschel et al., 1997; Masellis et al., 1998].

PHENOTYPE

The controversial findings of pharmacogenetic studies in schizophrenia may be related to several factors such as definition of response, duration of treatment, sample size, and ethnicity. It is generally agreed that a crucial prerequisite for verification of positive findings in independent studies is an exact and comparable phenotype characterization. Furthermore, it is likely that the majority of gene effects in response to medication will each individually be small, thus requiring the collection of large patient samples by multicenter studies. Practically, three aspects have to be taken into account: 1) patient characteristics; 2) definition of symptoms to be considered for response; and 3) assessment of response. Preliminary guidelines have been proposed by the 'Consensus Group for Outcome Measures in Psychoses for Pharmacogenetic Studies' [Rietschel et al., 1999].

Patient Characteristics

In addition to the core symptoms relevant to diagnosis, there are basic variables that should be accounted for when reporting results: a) demographics such as age, gender, and ethnicity; b) course of the disorder (e.g., age of onset); and c) history of prior treatment response.

Definition of Symptoms To Be Considered for Response

To describe the different aspects of response, specific symptoms (e.g., positive/negative symptoms, disorganization, altered affect, specific hallucinations and delusions) should be followed over the course of the investigation. In addition other measures of response can be assessed, e.g., neurocognitive functioning, psychophysiologic measures, motor behavior, hormone levels, quality of life.

Eventually, the crucial point for the identification of genes determining drug behavior will be the availability of large, well-defined patient samples.

Assessment of Response

Assessment of response requires specification with respect to: a) instruments to be applied; b) initiation; c) duration of the study; d) dose; and e) co-medication.

TABLE II. Genetic Variants of Serotonin Receptors

Receptor	Variant	Frequency*	Functional consequence	Reference
5-HT1A	Gly22Ser	2%	Agonist-promoted receptor downregulation ↓, inhibition of cAMP synthesis ↓	Nakhai et al., 1995; Rotondo et al., 1997
	Ile28Val	8%	No effect on agonist and antagonist binding and cAMP synthesis	Brüss et al., 1995; Erdmann et al., 1995; Nakhai et al., 1995; Rotondo et al., 1997
	Arg219Leu	<1%	?	Lam et al., 1996
5-HT1B	Phe124Cys	2%	Dihydroergotamine, sumatriptan and methysergide binding ↑, ketanserin binding ↓	Nöthen et al., 1994b; Brüss et al., 1999
5-HT2A	Thr25Asn	2%	?	Erdmann et al., 1996a
	His452Tyr	8%	Ca^{2+} mobilization ↓	Erdmann et al., 1996a; Ozaki et al., 1997
	−1437G/A	45%	Unclear	Spurlock et al., 1998; own results, unpublished
5-HT2C	Cys23Ser	13%	Serotonin and MCPP binding ↓	Lappalainen et al., 1995, Goldman et al., 1995
5-HT5A	Pro15Ser	6%	?	Iwata et al., 1998
5-HT7	Thr92Lys	<1%	?	Erdmann et al., 1996b
	Pro279Leu	1%	?	Erdmann et al., 1996b, Pesonen et al., 1998

*Frequencies apply to Caucasian populations if not otherwise stated.

PROSPECTS

The overall pharmacological effects of neuroleptic drugs are complex in nature and are likely to be determined by a combination of protein variants acting at the metabolic and the target level. Making a prediction of drug response at the level of the individual patient clearly requires a simultaneous look at a large number of genetic variants that are determinants of drug effects. The pharmacogenetic studies in schizophrenia discussed in this article still refer to a relatively narrow spectrum of genetic variants in drug metabolizing enzymes and drug targets. The main reasons have been the restricted number of genomic sequences for genes of potential pharmacogenetic relevance as well as the lack of information on their genetic variation. The rapid progress of the Human Genome Project, however, that will provide all human gene sequences in the very near future, recent advances in molecular sequencing technology, that enable large-scale identification of genetic variants such as SNPs, as well as high-throughput genotyping systems for these variants using DNA chip technology now makes it feasible to perform systematic pharmacogenetic studies. Recently, the genomics-company Celera Genomics has announced the identification of 20–30 million SNPs within the next 18 months. In a parallel effort, a powerful consortium of ten of the world's leading pharmaceutical companies together with the Wellcome Trust plans the identification of up to 300.000 SNPs in the human genome, that they regard as sufficient for most practical purposes [Masood, 1999]. From this plethora of genetic markers, future studies will have to identify the ones associated with drug response and adverse effects. This prospect for pharmacogenetics would only be affected by the development of new drugs that lack adverse effects and display superior efficacy in all treated patients.

After the field of pharmacogenetics is now about 40 years old, pharmacogenomics has entered the arena. Pharmacogenomics combines the basic concept of pharmacogenetics with the powerful new tools of genomics, thus enabling a broadened view at the entire spectrum of genes that determine drug behavior and sensitivity in schizophrenia. In the end, however, the crucial point for the identification of these genes will not be the technical prerequisites but the availability of large, exactly and comparably phenotyped patient samples.

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